Department of Health and Human Services
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National Cancer Institute

5th Meeting of the NCI-Frederick Advisory Committee (NFAC)
September 24, 2013

Summary Report

8560 Progress Drive
Auditorium Room E1600
Frederick, Maryland

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The NCI-Frederick Advisory Committee (NFAC) convened for its 5th meeting on 24 September 2013, in Auditorium Room E1600, 8560 Progress Drive, Frederick, MD. The meeting was open to the public on Tuesday, 24 September 2013, from 9:00 a.m. to 4:15 p.m. The NFAC Chairperson, Dr. Zach W. Hall, President Emeritus, Institute for Regenerative Medicine, University of California, San Francisco, CA, presided.

NFAC Members
Dr. Zach W. Hall (Chair)
Dr. J. Carl Barrett
Dr. David Botstein (absent)
Dr. Vicki L. Colvin (absent)
Dr. Levi A. Garraway
Dr. Joe W. Gray
Dr. Beatrice H. Hahn
Dr. Monica J. Justice (absent)
Dr. Lawrence J. Marnett (absent)
Dr. Jill P. Mesirov
Dr. Garry P. Nolan (absent)
Dr. Kenneth J. Pienta
Dr. Jennifer A. Pietenpol
Dr. Steven T. Rosen
Dr. Cheryl Willman

***Ex Officio* Members**
Dr. Stephen Chanock
Mr. John Czajkowski
Dr. James H. Doroshow
Dr. Paulette S. Gray
Dr. Douglas R. Lowy (absent)
Dr. Alan Rabson (absent)
Dr. Craig W. Reynolds
Dr. Robert H. Wiltrout

Executive Secretary
Dr. Thomas M. Vollberg

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I. CALL TO ORDER AND OPENING REMARKS

Dr. Zach W. Hall

Dr. Zach W. Hall, Chair, called to order the 5th meeting of the NFAC and welcomed the Committee members. After reviewing the charge to the Committee and the mission of the Frederick National Laboratory for Cancer Research (FNLCR), he reminded members of the conflict-of-interest guidelines and confidentiality requirements. Members of the public were welcomed and invited to submit to Dr. Thomas M. Vollberg, Executive Secretary, in writing and within 10 days, any comments regarding items discussed during the meeting. Dr. Vollberg reviewed the NFAC meeting schedule for 2014 and 2015.

Dr. Hall reflected on the progress made regarding the FNLCR since the inception of the NFAC in September 2011, including the recruitment of Dr. David C. Heimbrook as CEO of SAIC-Frederick (now part of Leidos Biomedical Research [henceforth Leidos]), the designation of the NCI-Frederick enterprise as the FNLCR, the completion and occupation of the Advanced Technology Research Facility (ATRF), and the recruitment of Dr. Frank McCormick as leader of the RAS initiative. Dr. Hall completes his term as NFAC Chair with the completion of this meeting, and Dr. Joe W. Gray, Oregon Health and Science University, will be the next NFAC Chair.

II. NCI DIRECTOR'S REPORT

Dr. Harold Varmus

Dr. Harold Varmus, Director, NCI, welcomed all and expressed gratitude to NFAC members for their service on this committee, especially Dr. Hall, who previously had provided consulting services to the Frederick enterprise and as NFAC Chair led a number of the changes to the laboratory, including the naming of the FNLCR. Dr. Varmus invited members to share candidate names to serve on the Committee.

Dr. Varmus reviewed the agenda, including the RAS project, which is changing the public's perception of the FNLCR. Members were reminded about other NCI work underway, namely through the Center for Global Health (CGH) in conjunction with the NCI-designated Cancer Centers, as well as genomic activities managed by the Center for Cancer Genomics (CCG), now headed by Dr. Louis Staudt. The NCI also is introducing genomic tools in the execution of clinical trials, matching conventional and immuno-chemotherapies as well as other targeted therapies. In addition, the Center for Biomedical Informatics and Information Technology (CBIIT), under the direction of Dr. George Komatsoulis, Acting Director, CBIIT, and Dr. Warren Kibbe, the new Director, CBIIT, is managing a cloud-computing pilot project that links high-quality informatics to clinical and genomic information. The NCI will join the Global Alliance, which will begin with cancer and eventually encompass other diseases.

Dr. Varmus remarked on the budget, stating that the NCI experienced a 5.8 percent reduction in FY 2013 from the FY 2012 level. Although the success rate was maintained, a recent poll found that approximately 40 percent of funded academic investigators managed the reductions to their grants by limiting their number of laboratory assistants.

III. RAS PROJECT UPDATE

Drs. Frank McCormick, David C. Heimbrook, and Atsuo Kuki

Drs. Frank McCormick, David C. Heimbrook, and Atsuo Kuki, Leidos, provided an update on the RAS project. They were joined by Dr. Ed Harlow, who described recent developments in the RAS community. The rat sarcoma viral oncogene homolog (RAS) encodes a protein that helps control cell growth, survival, and stability. There are four RAS types (Kirsten A and B [KRAS], Harvey [HRAS], and neuroblastoma [NRAS]), and the mutated form is found in 33 percent of human cancers (e.g., pancreatic cancer); currently is undruggable; and enables resistance to many existing therapies. Dr. Heimbrook reminded members that the RAS Program began with the exploration of the FNLCR's "National Missions" in May 2012, a RAS

workshop and the recruitment of Dr. McCormick in February 2013, enthusiastic approval by the NCI's National Cancer Advisory Board (NCAB) and Board of Scientific Advisors (BSA) in June 2013, and the Contract Office approval and establishment of the RAS Pivot in August 2013. The RAS Program will be implemented as a Hub-and-Spoke model that integrates those working on RAS; the FNLCR serves as the Hub and interacts with multiple Spokes (i.e., intramural laboratories, extramural NCI-supported laboratories, contract research, and biotechnology and pharmaceutical companies) to disseminate RAS knowledge widely across the country and create a RAS community of scientists through a virtual network.

Dr. Harlow provided insights into engaging the RAS community, commencing with efforts to identify and reach constituents by searching databases for National Institutes of Health (NIH)-funded RAS research as well as foundations—more than 1,700 grants in the United States deal with the RAS pathway. Interactions with investigators to develop an active network are planned through: email notifications by Dr. McCormick and a website to inform stakeholders about the progress of the RAS Program; a series of RAS-focused meetings sponsored by the FNLCR; and the development of a sophisticated "spider web" of the RAS intellectual structure based on words extracted from grant abstracts (e.g., disease sites, biological processes, gene families) to encourage greater interactions and collaborations among RAS researchers.

Members were informed that the RAS Program offers a new way of operating in that the contractor remains obliged in terms of transparency and accountability, but has greater latitude in accomplishing Program goals, such as management of program space at the ATRF and implementation of approved research plans. The result is an enhanced "pride of ownership" of the Program's success. Dr. Heimbrook said that an NFAC subgroup, chaired by Dr. Levi Garraway, has been established to provide strategic oversight to the RAS Program, and he reviewed the Program's prioritization and implementation governance. Funding for the RAS Hub is approximately $10 million, which comes from a reprioritization of ongoing activities, and the RAS Spokes will be funded through subcontracts or self-funded by partnering with pharmaceutical or biotechnology companies.

Dr. McCormick described seven projects focused on RAS mutations in human cancers, including pancreas, colorectal, and lung cancers (KRAS); acute myeloid leukemia and melanoma (NRAS); and bladder cancer (HRAS). Currently, there is no good strategy to deal with these mutations, particularly KRAS, which is found in 95 percent of human pancreatic cancers as well as 35–45 percent of human lung and colorectal cancers. The seven projects concern: target validation (Project Zero); direct focus on the RAS mutation (Projects 1–5); and the supply of high-quality, validated reagents (Project 6).

Project Zero provides the biological groundwork for other RAS studies by validating mutant KRAS as a target for tumor maintenance and identifying subsets of tumors in which KRAS is particularly important. Specifically, the project will determine the profile of tumors that respond to ablation of mutant KRAS along with pathways of acquired resistance to ablation, and develop a panel of cells to support drug discovery using shRNA cell lines or Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) technologies. Based on bioinformatics analyses of co-mutations that occur with KRAS, four mutated alleles (G12C, G12D, G12V, and G13D) have been selected for characterization. To provide cell culture support for Projects 1–5, wild-type and mutant RAS-less mouse embryonic fibroblasts (MEFs) will be used, with a focus on 4A-only versus 4B-only cells. In addition, human RAS-less cells will be developed in-house at the ATRF. The Project also will analyze data directly from human tumors and determine if the same signatures seen in special profiles from the isogenic cell lines are found in human tumors. A drug screen study of isogenic cell lines with RAS-less MEFs that interrogated pathways through rescue proliferation with either normal RAS isoforms or mutant KRAS alleles (G12V, G12C, G12D, and G13D) revealed different pathway signals upstream and downstream; in addition, the mutant alleles showed disparate clinical outcomes.

Project 1 aims to generate new structures for mutant KRAS alleles and complexes, and to identify allele-specific complexes that present therapeutic opportunities. Short-term activities will address protein analyses, pilot crystallization for KRAS variants, biophysical analysis of KRAS-Calmodulin interaction to

inform high-throughput screening assays, and characterization of KRAS allele complexes in human tumor cells via mass spectrometry. The frequency of mutant KRAS alleles in human pancreas, colorectal, and lung cancers totals an aggregate of 29,500 in G12C; 50,520 in G12D; 36,500 in G12V; and 13,440 in G13D, making KRAS a desirable therapeutic target. Understanding the mutant RAS structure will facilitate development of drugs to block crucial interactions between RAS and RAF proteins; few crystalline compounds are known to bind to KRAS. The priority for Project 1 is KRAS 4B alleles, which are the most frequent, particularly in human pancreatic cancer. Because differences in the C-terminus of KRAS 4B, NRAS and HRAS have made drug targeting challenging, the Project will use the protein Calmodulin to focus on KRAS selectivity.

Dr. McCormick told members that Project 2 will target KRAS selectivity through identification of compounds that inactivate KRAS independent of mutation status. The Project will acquire an assay developed by Dr. Mark Philips, qualify it for KRAS membrane association, and develop an intracellular Calmodulin assay. Project 3 will focus on disrupting KRAS protein complexes in cells and probe the nature of KRAS dimerization through photoactivated localization microscopy (PALM) imaging and single-molecule fluctuation techniques. Dr. McCormick noted a dearth of information about RAS and dimerization. Project 4 will provide a molecular description of the KRAS cancer cell surface to identify new targets for nanoparticle and antibody-mediated attack. Surface proteins will be used to deliver nanoparticles. In Project 5, RAS investigators will identify and validate KRAS synthetic lethal targets. Current synthetic lethal screening technology needs further development, and the Project will facilitate work that cannot be completed easily in academic settings. Project 6 aims to produce and validate high-quality reagents for the extramural community, including DNA clones, cell lines, viruses, antibodies, and proteins.

Dr. Kuki described the implementation of the RAS Hub, which focuses on pivoting strengths within the FNLCR contract to drive RAS projects, an effort referred to as the "RAS Pivot." The nine laboratories in the Advanced Technology Program (ATP) have been restructured to support the RAS Hub. Shared core laboratories (protein expression, protein chemistry, proteomics and mass spectrometry, molecular technology) provide advanced technical capabilities; imaging laboratories (optical and electron microscopy) operate in a blended mode of core and contract funding; and dedicated laboratories (nanotechnology, antibody, sequencing) operate under specific contract funding. In May 2013, Program staff analyzed HUB resources to identify capabilities and gaps as well as determine priorities (protein production, biophysics of protein complexes, novel cellular assays) and next steps (structural biology capability, expression analysis) to support the RAS Program. RAS Project Teams are being established, which will draw synergistically from the resources in the core laboratories. The core laboratories have been designed to maintain a breadth of capabilities and flexibility to support evolving project needs, and the RAS Project Teams can focus unencumbered on national program objectives. Dr. Kuki discussed the implementation steps, including the use of intramural core services, staffing the RAS Hub, Program coordination, and a cultural ecosystem transition to build an intellectual critical mass. The plan is to produce, validate, and distribute qualified and standardized biological reagents to the extramural community through Technical Service Agreements (TSAs). Next steps include the recruitment of RAS Project Team leaders, assistance to intramural laboratories in the use of the core laboratories, the hosting of RAS Program planning workshops at the ATRF, development of synergistic collaborations, and provision of reagents to the RAS Spokes. The FNLCR has several roles in enabling drug discovery, such as in therapeutics and diagnosis, RAS therapy mode of action, and new cell-based assays. Dr. Kuki said that through these roles, the FNLCR serves as a nexus for technology integration and applied science.

In the discussion, the following points were made:

- Members suggested that acute lymphoblastic leukemia (ALL) be considered for study by the RAS Project. The NCI-supported Therapeutically Applicable Research to Generate Effective Treatments (TARGET) Project on high-risk ALL has sequenced ALL tumors in the pediatric and young adult populations and found that nearly 30 percent of ALL cases have RAS mutations that are distributed equally among KRAS and NRAS.

- Members noted the importance of the cancer cell line context. An alternative approach for Project Zero is to use clean knockout mice and add 4A and 4B alleles in various CRISPR cancer cell lines to better identify contextual dependencies. In addition, because human epithelial cell lines are highly heterogeneous, biologic variations and heterogeneity should be considered when selecting the cell line and determining how to work the CRISPR technology within that cell line.

- Defining the mutant KRAS structure is essential for drug discovery. A full-length RAS protein structure is desirable but requires significant protein engineering.

- Members encouraged the RAS Program to support a global phosphoproteomics study in the setting of RAS perturbation to identify targetable partners and to study the efficacy of combined existing agents on RAS mutations. The Program could help investigators with RAS-targeting agents that have proved challenging. In addition, the Leukemia & Lymphoma Society has several vehicles for drug acceleration, including commercialization and target validation, which might be useful in facilitating access to potential therapeutics.

- The RAS Program should consider leveraging The Cancer Genome Atlas (TCGA) and Clinical Proteomic Tumor Analysis Consortium (CPTAC) colorectal cancer data for the proteome and mining the cell surface protein and secretome from that dataset to cluster KRAS mutants versus normal.

- Members expressed enthusiasm for the RAS Program and its direction and encouraged the NCI and FNLCR leadership to promote the RAS study as a model for other investigations.

- Members suggested that the Program should engage Centers of Excellence, the computational community, measurement scientists and advanced technology developers, and other non-RAS communities as appropriate.

- Dr. McCormick clarified that input from the extramural community will be welcome in all of the RAS Projects either through direct collaboration or in an advisory level. Communications will be sent to all those known to be involved in RAS studies to engage their input.

- Members encouraged the Program to engage the pharmaceutical industry and academia to share experiences and pre-competitive data as well as learn from failures.

IV. RECOGNITION OF CHAIR

Dr. Harold Varmus

Dr. Varmus expressed appreciation to Dr. Hall, retiring NFAC chair, for his dedication and service in leading the NFAC from its inception through the past 2 years.

V. TOUR OF THE ATRF LABORATORY

Mr. Hoyt Matthai and Dr. Dwight V. Nissley

Mr. Hoyt Matthai and Dr. Dwight V. Nissley, ATRF, guided the NFAC members on a tour of the ATRF laboratory.

VI. FFRDC BEST PRACTICES: LEARNING FROM OTHER FFRDCs

Dr. David C. Heimbrook and Mr. John Czajkowski

In February 2013, FNLCR leadership and the NFAC visited the Lawrence Berkley National Laboratory (LBL). Dr. Heimbrook described lessons gained from this visit that could be applicable to the

FNLCR, as well as visits to other Department of Energy (DOE) laboratories, specifically the Sandia, Lawrence Livermore, and Jefferson National Laboratories; other interactions with DOE national laboratory leadership; and external reviews of the DOE FFRDCs. These national laboratories differ from the FNLCR in that they: provide the science for all of the DOE; compete for funding; offer a distinctive "user facility" that is a draw for the extramural community; and have access to Congressionally mandated Lab-directed Research and Development (LDRD) funds.

Dr. Heimbrook reminded members that the LBL focuses on material science, biology, and computation, with an emphasis on the biosciences. Its co-location with the University of California, Berkley (UCB), is essential to its culture and science, and UCB reinvests most of its earned award fee in the LBL. Characteristics of the LBL include: a significant institutional "pride of ownership" with a modest onsite government presence; most major projects start with LDRD funding; and in some areas a tenure like-system for investigators begins with a 5-year internship. In addition, there is extensive collaboration and funding from external sources as well as strategic effort to expand commercial access to LBL capabilities. Dr. Heimbrook explained that the Lawrence Livermore and Sandia laboratories have closer government interface in contractor operations, and relationships with regional universities are important but not as integrated as at the LBL; the highly entrepreneurial atmosphere and LDRD characteristics for each laboratory also were noted. The Lawrence Livermore National Laboratory uses several partnering mechanisms, including Contractor Cooperative Research and Development Agreement (cCRADA); Work for Others; and Advancing Commercial Technology, which contracts with partners directly without government involvement. Two published reviews of the DOE FFRDCs ("DOE Management and Oversight of FFRDCs reviewed by the National Academy of Public Administration," January 2013; and "Reimagining the National Labs in the 21st Century," June 2013) recommended a focus on key outcomes, unified laboratory stewardship, contractor accountability, and better incentives to move technologies to the market.

Key opportunities for the FNLCR illuminated by the DOE and NASA FFRDC experiences are to build strong ties to local academic institutions and to recognize that entrepreneurial science is enabled by the academic mindset and ownership of the project. In addition, venture funding of entrepreneurial science is important, and a Contract Assurance System will enable contractor accountability without requiring transactional oversight or micromanagement. Dr. Heimbrook indicated that he will continue to engage with and visit other FFRDC laboratories.

In the discussion, the following points were made:

- Members encouraged FNLCR leadership to incorporate a program similar to the LDRD for both the FNLCR laboratories and scientific programs, such as the RAS Program. The DOE and NASA LDRD Programs serve as a catalyst for innovation and collaboration with academic partners, are highly competitive and internally peer reviewed, allow investigators to consider their scientific direction from a 5–10 year perspective, and are ideal for tackling short-term, challenging projects.

- Members voiced strong support for the development of strategic ties between the FNLCR and local universities, observing that the LBL's vibrant connection with the UCB appears to be the "special sauce" in the LBL's high-quality work and reputation as a world-class FFRDC. The NCI should consider incentives for partnerships between the FNLCR and these universities to strengthen the FNLCR's function as an FFRDC. Champions should be identified at each university, and strengths brought by each academic organization should be considered to best leverage expertise and interest. Collaborative opportunities, such as lectures, internships, and postgraduate fellowships, could enrich the relationship between the FNLCR and the local universities.

- The DOE's LDRD funding encourages investigators to consider how laboratories would participate in developing scientific areas of interest to the DOE. Most of the LDRD funds are strategically deployed

and provide a means to engage the laboratories in thinking scientifically about how to prepare for the next opportunity.

VII. NEW SCIENCE ENABLED BY NEW PARTNERING MECHANISMS

Dr. Jeffrey D. Lifson

Dr. Lifson, Director, AIDS and Cancer Virus Program (ACVP), FNLCR, discussed the impact of effective partnering mechanisms between intramural and extramural scientists and institutions. The research being facilitated through these mechanisms includes nonhuman primate studies to advance aspects of AIDS research. At last year's NFAC meeting, Dr. Lifson presented an overview of the ACVP research highlights as well as the science support cores, which have been expanded over time to provide unique and specialized services in support of internal as well as external research projects.

Although the provision of core services to the broader research community previously was limited by funding and required alignment with NCI's priorities, two new FNLCR collaborative outreach partnering mechanisms have been developed to allow the provision of core service support to extramural investigators who pay for the services from their grants. These mechanisms, which were implemented in response to guidance provided by the NFAC, include the Technical Services Agreement (TSA) and the cCRADA. The TSA is a standardized, streamlined process executed under the CRADA statute to provide well-defined, established but unique specialized research services to the extramural scientific community. Currently, 23 TSA services have been approved to reduce "administrative viscosity" and efficiently utilize available services. The cCRADA is utilized to streamline direct research collaborations between a contractor and external research party when government personnel are not involved in the cooperative research. Processes for generating, reviewing, and approving proposals have been established. Three cCRADAs and 59 TSAs have been executed to date.

Dr. Lifson presented an update regarding ongoing research collaboration with Dr. Louis Picker at the Oregon National Primate Research Center (ONPRC) to study the protective efficacy of vaccine responses. Cytomegalovirus (CMV) infection generates an unusual immune response, and specialized vectors might provide more protection than typical vaccines. Strikingly, inoculation of animals with the specialized Rh-CMV/SIV generates a distinct form of vaccine protection in which an initial infection (confirmed with virological and immunological evidence) is controlled over time with eventual aviremia. The CMV vectors generate negligible antibody responses and antibody-mediated protective effects; rather, broad and extended immune responses are biased toward the memory effector phenotype. Dr. Lifson's team hypothesized that a persistent immune response might control the local and generalized viral infection.

Recently, the researchers analyzed the immune responses in greater detail. Reproducible experiments showed that the CD8+ T cell immune responses induced by the Rh-CMV/SIV vectors are not consistent with those induced by conventional vaccines or natural infection with SIV. Additionally, there is an extraordinary breadth of the induced CD8+ T cell responses to the Rh-CMV/SIV vaccine. When the vaccine peptides were truncated to identify the minimal epitope required for response, the reactivity of approximately 2/3 of the response by CD8+ T cells was optimal for epitopes of 11 to 13 amino acids in length, which appears similar to a classical MHC class II (MHC-II) restricted CD8+ T cell response. Blocking experiments followed by intracellular cytokine staining corroborated the idea that the Rh-CMV/SIV induces an MHC-II response. Furthermore, multiple MHC-II allomorphs can present the same peptides, indicating a broad presentation promiscuity and evidence of "supertopes." The unusual properties of the CD8+ T cell responses likely derive from a vector-dependent pattern of antigen presentation. Importantly, engineering vectors based on these properties might improve the optimization of desired vaccine responses.

Dr. Lifson described studies that extended the successful intrarectal vaccine administration to intravaginal and intravenous challenges. The infection, including virus disseminated to tissues, is progressively cleared over time (mediated by persistent immune surveillance), leading to a functional cure with an absence of

measurable virus. Longitudinal analysis of viral load in numerous tissues (e.g., bone marrow, lymph nodes, spleen) confirmed the presence of initial viral replication that was ultimately controlled and cleared in the majority of the animals. To confirm the absence of virus, Dr. Lifson's team used adoptive transfer of cells from animals that had cleared the infection into naïve hosts, all of which showed no evidence of virus.

The unusual immunology of the Rh-CMV/SIV vectors and progressive clearance of virus over time via broad and atypical immune responses suggest that this approach might be advantageous from a therapeutic as well as prophylactic perspective. As effective as combination retroviral therapy can be under optimal circumstances, lifelong treatment of all infected people worldwide is not a viable approach; developing potential novel therapeutics, such as this type of vaccine, will be important. The next step is a proof-of-concept study for a formal therapeutic approach. Preliminary results indicate that even in animals that are infected for a long time with the virus, vaccination induces new CMV vector-mediated responses similar to those seen in prophylactic vaccine studies.

In the discussion, the following points were made:

- The impetus of the collaboration between Drs. Lifson and Picker originated from the lack of progress in the HIV vaccine field and the desire to try a novel approach with an agent that elicits a qualitatively different immune response. The ACVP has developed nationally recognized expertise in virologic monitoring of nonhuman primate species. The *in vivo* and immunology experiments were conducted at the ONPRC, while the virologic analysis (e.g., monitoring of plasma viremia and tissue viral load) was conducted at the FNLCR.

- The ultra-sensitive virologic assays developed by Dr. Lifson's team to demonstrate the absence of viral load are unprecedented. Each experiment evaluates more than 70 tissues with multiple replicate samples.

- The NFAC's contribution to enabling the partnering mechanisms between the FNLCR and outside partners was useful to this project and laid the groundwork the spokes of the RAS project hub and spoke model. Dr. Heimbrook and the other FNLCR leaders were recognized for effectively functionalizing the partnership mechanisms.

- A literature search reveals rare instances of occasional MHC-II restricted alloreactivity mediated by CD8+ T cells, but nothing similar in scope to the broad and general vector-dependent responses generated by the Rh-CMV/SIV vector.

VIII. PROPOSED ORGANIZATIONAL CHANGE: DIVISION OF EXTRAMURAL ACTIVITIES

Dr. Paulette S. Gray

Dr. Paulette S. Gray, Director, Division of Extramural Activities (DEA), announced the intent to reorganize several components of the DEA. Following new requirements within the Department of Health and Human Services (HHS) and NIH, reorganization of a division component must be published in the *Federal Register* and presented at two open meetings. Members were informed that the DEA's Special Review Logistics Branch will be abolished, and from that three Branches will be created: Research Technology Review Branch; Special Review Branch; and Division of Process and Distribution Unit. In addition, the DEA Committee Management Office (CMO), which has been in existence for approximately 40 years, is being formally established. Dr. Gray noted that these reorganization components do not require additional full-time equivalent (FTE) or staff. Following her presentation, there were no issues/concerns expressed regarding the proposed organization change.

IX. PROGRESS WITH PATIENT-DERIVED MOUSE XENOGRAFTS

Dr. James H. Doroshow

Dr. James H. Doroshow, Deputy Director, informed members about a preclinical models repository to support cancer discovery and therapeutics development. The patient-derived mouse xenografts (PDX) repository would support a national program to provide clinically annotated and molecularly characterized PDX models in multiple tumor types to extramural investigators. Dr. Doroshow noted that preclinical models are expensive to develop and maintain but are critical to enhance reproducibility and transparency of preclinical data, allow comparative assessment of molecular predictors of drug efficacy, and provide proof-of-mechanism pharmacodynamics. The NCI currently funds a large network of early phase academic trial sites to supply tumor samples, and clinical annotation of specimens for patients on therapeutic trials are integral to NCI studies. A principal goal is to ensure access to models and baseline molecular and clinical data for the extramural community. Long-term aims are to compare PDX, conditionally reprogrammed lines, and other new culture systems to current xenograft models to optimize drug development across several histologies and/or genotypes. Another goal is to understand the mechanisms of drug resistance in patients using multiple model systems that allow comparison with clinical trial outcomes.

In establishing a quality-controlled repository of PDX models that have undergone molecular characterization, the NCI would seek intellectual input from academia and the pharmaceutical industry. Conditionally reprogrammed cell lines (i.e., tumor and adjacent normal tissue) coming from metastatic lines would be co-developed. Members were told that both solid and liquid tissues would be obtained from NCI-designated Cancer Centers and NCI intramural clinics for new models as well as PDX models that are currently available from pharmaceutical and biotechnology companies and the Cancer Centers. More than 1,000 models would be produced, with clinical annotations that reflect genetic diversity and effects of therapy for application in target qualification, pharmacodynamics assay and predictive marker development, and "preclinical" clinical trials. The PDX repository would include approximately 75–100 unique patient samples per common disease to sufficiently power subsequent validation or efficacy studies, and comprehensive pre-competitive molecular characterization of samples and earliest passage PDXs would be completed when data are not available.

Dr. Doroshow shared examples of how tissue outputs from a Molecular Profiling-based Assignment of Cancer Therapeutics (MPACT) clinical trial were incorporated into the PDX model as well as histologies of multiple generations of a colorectal cancer specimen and variations of gene expression across passages of bladder cancer and glioblastoma. Members were updated on the initial progress in tissue/model acquisition. Sixteen NCI-designated Cancer Centers agreed to supply 20 tumor and matched blood samples with clinical annotation in FY 2014, with a focus on less common malignancies, for a total of 300 tumors and 300 blood samples. In addition, Cancer Center collections have been offered, more than 300 unique PDXs are being negotiated with pharmaceutical and biotechnology companies, and the NCI MPACT trial will provide more than 1,000 tumor biopsies.

In the discussion, the following points were made:

- One-half of the PDX models will be developed at the FNLCR, from biopsies obtained from NCI-supported clinical trials, as new models of metastatic disease. The protocol for acquisition into the model will require detailed clinical annotation at the time of tissue excision. The FNLCR likely will perform genomic characterization of some clinically annotated samples from external sources. Fully formed samples will come from pharmaceutical and biotechnology collaborators or from some NCI-designated Cancer Centers that already have characterized their samples to place in the repository.

- The initial acquisition phase will focus on samples of diseases that are dramatically underrepresented in PDX libraries (e.g., sarcomas, bladder cancer).

- A PDX collection of a subset of tumors with RAS mutations ready for testing could serve as a primary source of human tissues for the RAS project.

- Dr. Doroshow clarified that although detailed analysis on every passage would be cost prohibitive, trust in the use of the repository will be ensured by completing full characterization of the passages that will be expanded to distribute to the extramural community.

- Members expressed enthusiasm for the PDX model and noted its promising application for fundamental cancer biology studies.

- Members discussed the CTC technology. Dr. Doroshow shared examples of CTC-derived PDXs that looked genetically like the parental tumor and said that profiling of one of his patients showed that they were the same. In addition, development of CTC outgrowth technologies is underway and the NCI should begin considering the best technology to adopt.

- Members encouraged the NCI to support a question-driven project to demonstrate the efficacy of the PDX model and thus show the utility of generating a large number of therapeutic reagents.

- The NCI should consider a preclinical/clinical trial of HRAS-mutant bladder cancer using a novel agent brought into the RAS Program.

- The first goal is to provide these materials at a modest cost to the extramural community, including academia and pharmaceutical and biotechnology companies. The library will be developed over the next year, with distribution commencing once an adequate catalog is established.

X. CLOSING DISCUSSION AND A LOOK AHEAD

Drs. Zach W. Hall and Joe W. Gray

Dr. Gray thanked Dr. Hall for setting the stage for going forward. He observed that issues remain, including the relationship between the contractor Leidos and the NCI, including communication, linkages with venture capital, and the planning and community engagement process for the FNLCR. Other areas to discuss are FNLCR ties with academic partners, the identification and funding of additional research opportunities within the context of an FFRDC, such as high-information content clinical trials, mechanisms for heterogeneity, and reagent development; support for transformative technologies; the development of the FNLCR as a knowledge center on specific areas; and the planning, review, and scientific community engagement process for the FNLCR. Members were encouraged to submit additional topics for discussion at future meetings.

In the discussion, the following points were made:

- The NCI has engaged the scientific community in FNCLR activities through ongoing dialogues and presentations with its advisory boards, the NCAB and BSA, as well having NCAB members serve on the NFAC.

- Members encouraged the FNLCR leadership to implement a proactive communication strategy that strengthens the growing trust and interest in the national laboratory and informs the scientific community about the FNLCR contractor status, support, and capabilities.

- NFAC should consider meaningful projects for the FNLCR to undertake, as well as the optimal level of service functions provided to both the intramural and extramural communities and the best metrics for the science projects conducted at the FNLCR.

- Members noted that a successful RAS Project will serve as a model for future projects but suggested a conservative approach to starting additional large ventures to allow tangible outputs from the RAS studies.

- Members recognized that the FNLCR and other FFRDCs provide high-visibility technology development, including hardware, expertise, and support, that scientific researchers need and cannot access elsewhere.

IX. ADJOURNMENT
Dr. Zach W. Hall

Dr. Hall thanked the Committee members and other invitees for attending. There being no further business, the 5th meeting of the NFAC was adjourned at 4:15 p.m. on Tuesday, September 24, 2013.

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Date Zach W. Hall, Ph.D., Chair

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Date Thomas M. Vollberg, Ph.D., Executive Secretary